From: Drozdowicz,Bronek Z.
Sent: Tuesday, September 3, 2002 1:27 PM
To: 'masten@niehs.nih.gov'
Subject: Response to the NTP request for information about NF3
Importance: High

Dear Scott,

As I have told you in our conversation of August 23rd, 2002, Air Products and Chemicals, Inc. is a major manufacturer of NF3. We do have certain health hazards data on this material that should be of interest to your organization since the NTP Interagency Committee for Chemical Evaluation and Coordination recommended NF3 to be tested. The FR June, 2002 notice of contained a request for toxicological, production and use information on this material in order to make a final determination whether the NTP will conduct any studies on NF3.

I attach for your information a fairly detailed summary of the toxicological properties of NF3 (including data from Air Products internal studies) as well a some relevant information about NF3 production and its uses.

Hope this information will be helpful to NTP in its deliberations. Please feel free to contact me if you have any questions.

Regards,

Bronek Z. Drozdowicz, PhD

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Air Products and Chemicals, Inc.
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Office 610 481 4620
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<<020828 NF3 tox profile 7783-54-2.pdf>>
<<020830 NF3 summary.pdf>>

From: Drozdowicz,Bronek Z.
Sent: Friday, October 25, 2002 10:39 AM
To: 'masten@niehs.nih.gov'
Subject: Updated NF3 documents
Importance: High
Message Flag: For Your Information
Flag Status: Flagged

Scott,

I attach copies of the two summary NF3 documents you have requested.
They have the same text but the "confidential" stampings have removed.
Hope that helps.

Best regards,

Bronek
<<022528 APCI NF3 summary.doc>> <<021025 APCI NF3 tox profile 7783-54-2.doc>>

NITROGEN TRIFLUORIDE: PRODUCT SAFETY OVERVIEW

CAS# 7783-54-2

Uses: Nitrogen trifluoride (NF3) is used as an oxidizer of high energy fuels, for the preparation of tetrafluorohydrazine, and for the fluorination of fluorocarbon olefins. The major use of NF3 is in the manufacture of semiconductors, where it is used to clean CVD chambers.

Physical Properties: NF3 is a harmful, nonflammable, oxidizing, compressed gas. The gas is odorless, but may contain contaminants that can impart a musty odor.

Toxicity: The LC50 for NF3 is 6700 ppm for a 1 hour exposure in rats. This means that half of the rats exposed to this level of NF3 for a period of one hour would be expected to die within a 14 day period.

The IDLH value for NF3 is 1000 ppm. At this level, human exposure for up to 30 minutes would not be expected to result in death or permanent adverse health effects. Adverse health effects that are treatable or resolve spontaneously over time would be likely to occur. In the case of NF3, exposure at this level would likely result in methemoglobinemia and hemolytic anemia. Methemoglobinemia will usually resolve spontaneously over several hours while hemolytic anemia may take weeks to resolve. In severe cases, medical treatment may be required for both conditions.

The TLV for NF3 is a TWA of 10 ppm. At this level, humans exposed to NF3 for 8 hours per day, 5 days per week would not be expected to have any adverse effects. The 10 ppm value for NF3 was based on a subchronic inhalation study that was conducted in rats. In the study, rats that were exposed to 100 ppm of NF3 for 7 hours per day, five days per week for 19 weeks developed pathological changes in their livers and kidneys. The ACGIH incorporated an additional safety factor of 10 to account for longer exposure periods when setting the TLV.

There are no human or animal studies demonstrating carcinogenic effects following NF3 exposure. ACGIH, IARC, NTP, and OSHA do not list nitrogen trifluoride as a carcinogen.

NITROGEN TRIFLUORIDE: TOXICOLOGY PROFILE

CAS#: 7783-54-2
Revision Date: June 27, 2002
Synonyms: NF_3
Structure:

ACUTE TOXICITY:

- **Oral LD_{50}:** No data found
- **Dermal LD_{50}:** No data found
- **Inhalation LC_{50}:** 6700 ppm (1 hr) (rat)[1,2,5]; 2000 ppm (4 hr) (mouse).[1,2]

For all species tested, the immediate effect of acute exposure to high concentrations of NF_3 is extensive methemoglobin formation with subsequent hypoxia, cyanosis, and dyspnea (difficult or labored respiration).[1,3,4,5] This is often followed by hemolytic anemia, which can cause liver, kidney, and spleen effects.[2,3,4,5]

Rats that received a single (8-15 ml/kg) intraperitoneal injection of nitrogen trifluoride gas became cyanotic and developed enlarged spleens.[4] Dogs surviving a 60 minute exposure to 9600 ppm NF_3 developed Heinz bodies (dark-staining globules on red blood cell membranes), red blood cell hemolysis, and anemia.[2,4,5] Vomiting has also been observed in dogs and monkeys that have inhaled nitrogen trifluoride gas.[4]

Rats died after inhaling 10,000 ppm for 60 to 70 minutes (600,000-700,000 ppm x min). Death occurred in rats during a 4 hour exposure to 2500 ppm. 1000 ppm for 4 hours regularly produced methemoglobinemia, while a 10 minute exposure to 3000 ppm (30,000 ppm x min) failed to generate measurable amounts of methemoglobin.[3] At 30,000 ppm x min, no anemia or other toxic effects were discernible in exposed dogs. At 120,000 ppm x min severe anemia occurred in dogs.[5] In lethal exposures up to 80% of the total blood pigment may be found as methemoglobin. In non-lethal exposures the methemoglobin spontaneously reverts back to hemoglobin over several hours. In contrast, the consequences of an intense Heinz body hemolytic reaction, ie, decrease in hematocrit, hemoglobin, and red blood cell counts, may be manifested for 20 to 40 days.[3,5]

IRRITATION:

- **Eye:** Slight Irritant[3,4,5]
- **Skin:** No data found; no irritation is expected
- **Respiratory:** No data found
- **Sensitization:** No data found

SUBACUTE/SUBCHRONIC TOXICITY:

Rabbits that were administered 9 intraperitoneal injections of 10 mls of NF_3 gas in 29 days showed enlarged spleens, pathological changes in the liver, and heart muscle degeneration.[4]

Rats were exposed to NF_3 concentrations of 0, 20, 100, and 500 ppm for 6 hrs/day, 5days/week for 2 weeks. Following the tenth exposure, blood was collected and the animals were sacrificed. Rats in the 500 ppm group showed severe to moderate hemolytic anemia. Rats in the 100 ppm group exhibited milder hemolytic anemia. Microscopic changes were noted in the liver, kidneys, spleen and bone marrow of the 500 and/or 100 ppm animals. The pathological effects were considered secondary responses to hemolytic anemia. No effects were observed at 20 ppm.[12]

Rats were exposed to nitrogen trifluoride via inhalation 6 hrs/day, for 28 days in a Japanese study. Effects, such as darkening, tumescence, and increased hemosiderin granules, were observed in the spleen at $\geq$ 10 ppm. 2 ppm was the NOEL.[6]

Rats exposed to NF_3 via inhalation 7 hrs/day, 5 days/week for 19 weeks at 100 ppm exhibited mild to moderate pathological changes in the liver and kidneys. Kidney changes appeared consistent with fluoride toxicity. No effects on hematological parameters or on the spleen were seen. There was no evidence of fluorosis in the teeth or bones.[2,3,4]

GENOTOXICITY:

Unpublished results of in vitro genotoxicity testing of NF_3 samples of various origins in the USA (Air Products - 1986) and Japan (Japanese Bioassay Center - 1989) indicated a possibility of NF_3 having mutagenic properties. The genotoxic potential of the present high-purity commercial NF_3 was investigated using current testing protocols. NF_3 was examined for mutagenic activity in the Ames' Salmonella typhimurium and Escherichia coli assays. The tests were performed with Salmonella strains TA1535, TA98, TA100, and TA102 and E. coli strain WP2 (uvrA). NF_3 was tested (with and without an Aroclor-1254-induced rat liver metabolic activation system) at 0.1, 0.25, 0.5, 1.0, 2.0, and 5.0 molar percent dose levels. NF_3 was not found to be mutagenic under the test conditions used.[7] In a repeat assay using the same test conditions, NF_3 elicited a weak, mutagenic response.[9]

NF_3 was also evaluated for mutagenic activity in a mouse lymphoma cell assay. NF_3 was tested (with and without an Aroclor-1254-induced rat liver metabolic activation system) at dose levels of 1, 2, 4, 6, and 10 percent in an atmosphere of 5% CO_2 in air. Although there appeared to be an increase in average mutant frequency with increasing concentration of NF_3, there were no statistically significant increases in mutant frequency at any concentration either with or without metabolic activation.[9]

NF_3 was examined for clastogenic activity in the in vivo bone marrow micronucleus test in Swiss-Webster mice. Fifteen mice per sex per treatment level were exposed to NF_3 concentrations of 842, 1277, or 2474 ppm. A negative control group was exposed similarly and concurrently to cylinder air. A group of 15 male mice was treated by gavage with 300 mg/kg of urethane in water (positive control) on the same day as the inhalation exposure. Five mice per sex were sacrificed 24, 48, and 72 hours after exposure. Bone marrow smears were prepared from each mouse. The number of micronucleated polychromatic erythrocytes (PCEs) in at least 1000 PCEs per animal, and the number of PCEs in at least 200 erythrocytes per animal, which provides an index of cytotoxicity, were analyzed. A statistically significant increase in micronucleated PCE was observed in male mice at 72-hr after exposure to 842 ppm of nitrogen trifluoride and in female mice at 48 hours after exposure to 1277 or 2474 ppm. Because the increase in the male mice was not dose-related and the control animals for the female mice had a very low micronucleus frequency, additional analyses were performed. The frequency of micronuclei in 2000 PCE from all animals in the range-finding assay and the frequency of micronuclei in an additional 2000 PCE from the 48-hour female dose groups of the definitive experiment were determined. No significant increase in micronucleated PCE was found in the additional analyses. Therefore the high purity nitrogen trifluoride was determined to be non-clastogenic in the mouse bone marrow micronucleus assay.[7]

RISK ASSESSMENT:

The ACGIH Time Weighted Average (TWA) is 10 ppm (29 mg/m^3).[8] The NIOSH Immediately Dangerous to Life and Health (IDLH) value is 1000 ppm.[10] The National Academy of Sciences - National Research Council, Committee on Toxicology recommended Emergency Exposure Limits (EEL) for NF_3 of 2,250 ppm for 10 minutes, 750 ppm for 30 minutes, and 375 ppm for 60 minutes or 22,500 ppm x min.[11]

HUMAN INFORMATION:

Symptoms include dyspnea, cyanosis, weakness, dizziness, headache, confusion, and other manifestations associated with a reduced oxygen supply to body tissues.[3,4,13]

Skeletal fluorosis is possible from chronic exposure. Intake of more than 6 mg of fluoride per day can result in fluorosis. Symptoms of fluorosis are weight loss, anemia, weakness, general ill health, brittleness of bones, and stiffness of joints.[14] The U.S. EPA has calculated that the development of crippling skeletal fluorosis requires the consumption of 20 mg or more of fluoride per day over a 20 year period (i.e. 0.28 mg/kg/day) and considers intake of 0.12 mg/kg/day of fluoride to be a safe exposure level.[15]

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Air Products and Chemicals Inc.

NF3: Production and Use Summary

Nitrogen Trifluoride (NF3) is a toxic, colorless, odorless, non-flammable, oxidizing compressed gas filled by APCI to a pressure of 1450 psig. NF3 offers the advantage of relative ease of use at ambient conditions and the ability to act as a fluorinating agent. Because of these factors, NF3 has gained commercial acceptance in a number of applications.

The semiconductor industry uses it in plasma and thermal applications for its advantages such as high etch rates, high selectivity, carbon-free etching, and minimal residual contamination. NF3 is also used as a fluorine source in high-energy chemical lasers, owing to its ease of use relative to fluorine gas and as an intermediate in the production of specialized chemicals. Estimated world production for 2002 is 5,000,000 pounds.

Air Products manufactures NF3 at its Electronics Specialty Gas facility in Hometown, PA. Our NF3 production equipment has been in operation for 26 years without any serious safety incidents.

Our production facility is operated from a control room that is a separated from the production room. Even though there are no established industrial hygiene methods for monitoring NF3, we use continuous infrared area/alarm monitors in production areas for the purpose of detecting upset conditions. The bulk fill operations are located out of doors and the cylinders are filled in a ventilated and monitored clean room. The operators are located in the control room for most of the fill operation. We have no records of any personnel exposure incidents related to the production and fill of NF3.

Customers using the product locate the bulk containers outside and cylinders are located in gas cabinets inside Hazardous Process Materials rooms. These cabinets are ventilated and monitored. The product is piped to tools located in clean rooms that are ventilated and monitored. The NF3 is mostly disassociated during use and the reactive byproducts scrubbed from the exhaust. We are unaware of any adverse exposure issues for NF3 within our customer base.